Iatrogenic autoimmune progesterone dermatitis treated with a novel intramuscular progesterone desensitization protocol

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Clinical Implications

- Iatrogenic autoimmune progesterone dermatitis is a rare disorder precipitated by the administration of exogenous progesterone.
- Novel desensitization with intramuscular progesterone in oil offers a fertility-sparing therapeutic option, particularly in women undergoing *in vitro* fertilization.

TO THE EDITOR:

Autoimmune progesterone dermatitis (APD), or progesterone hypersensitivity, is a rare disorder caused by an immune response to progesterone.[1-3] It was first described by Géber in 1921 and is characterized by cyclic cutaneous eruptions that occur during the luteal phase of the menstrual cycle, coincident with peak endogenous progesterone.[1-7] The rash develops 3 to 10 days before onset of menses and regresses or resolves after menstruation cessation.[1-4] The skin eruptions most commonly manifest as urticaria; however, the presentation is variable, and cutaneous lesions may also include erythema multiforme, folliculitis, purpura, stomatitis, eczema, angioedema, papulovesicular eruptions, and vulvovaginal pruritis.[1-6]

The literature primarily reports cases of cyclic APD related to endogenous progesterone, although cases are documented of local and systemic reactions related to exogenous exposure, suggesting isolated hypersensitivity to synthetic progesterone.[1,5] Women undergoing *in vitro* fertilization (IVF) are exposed to high doses of exogenous hormones which may induce hypersensitivity, leading to iatrogenic APD.[1]

The cutaneous lesions of APD are resistant to antihistamine and corticosteroid therapy.[3,6] Conventionally, patients are treated by way of ovulation suppression; however, definitive treatment is hysterectomy and oopherectomy.[1,6] Desensitization offers a therapeutic option in women with APD who wish to maintain their fertility and also in women who are undergoing infertility treatment.[1,7] To our knowledge, no cases are reported in the literature of rapid desensitization with intramuscular progesterone. We report a case of iatrogenic APD induced by synthetic progesterone in association with IVF and describe a novel desensitization protocol with intramuscular progesterone in oil (PIO).

CASE REPORT

A 26-year-old gravida 3, para 0 woman at 7 weeks of gestation after IVF presented to the University of Arizona Allergy and Immunology Clinic for evaluation of urticaria that developed after intramuscular PIO injections. The urticaria developed within 2 minutes of each PIO administration and lasted for approximately 2 hours, resolving without bruising. Early in her therapy, she would develop a cluster of urticaria at the injection site. With each subsequent injection, the reaction became more diffuse, and she eventually developed concurrent urticaria on her thighs, abdomen, and buttocks. She reported no other systemic symptoms.

As an alternative to intramuscular progesterone preparations, she had been prescribed intravaginal progesterone suppositories (Crinone and Endometrin) and progesterone cream that resulted in vaginal irritation characterized by burning, pruritus, and the formation of blistering lesions, suggestive of a delayed hypersensitivity reaction. Her obstetrician advised her that these preparations did not result in a significant rise in her progesterone levels. She would therefore require daily injections of 50 mg PIO for 5 additional weeks to support this pregnancy. Pertinent medical history included recurrent IVF failure and allergic rhinitis.

On the day of presentation, the patient did not have skin lesions present; however, she provided photographs of her typical cutaneous eruptions consistent with urticaria. In light of her clinical presentation, progesterone hypersensitivity was suspected. Skin prick testing was performed with the patient's own full-strength progesterone in sesame oil, 50 mg/mL (American Regent, Shirley, NY), and sesame extract, with saline and histamine controls. Results read at 15 minutes showed a 3-mm wheal and >20-mm flare to PIO. Skin prick testing to sesame extract was nonreactive. She was therefore diagnosed with immediate hypersensitivity to progesterone. Although delayed type hypersensitivity to topical progesterone was also suspected according to her clinical history, confirmatory patch testing was deferred.

Treatment selection for this gravid patient raised a therapeutic dilemma, because traditional therapies for APD were not feasible. Recently, Prieto-Garcia et al[1] reported the successful treatment of APD by way of rapid desensitization with intravaginal progesterone suppositories in three women undergoing IVF. For our patient, however, in addition to causing severe local reactions, intravaginal progesterone preparations did not sustain a significant rise in her progesterone levels. As a therapeutic alternative, we adapted previously described drug desensitization protocols[1,8,9] to design a novel 13-step, rapid desensitization protocol that used intramuscular PIO (Table I). The target dose was 50 mg daily. She received 13 incremental doses of intramuscular PIO administered in the deltoid muscle. Injections were alternated between arms with each administration and dose escalation occurring every 15 minutes.

The patient tolerated the desensitization procedure without evidence of hypersensitivity reaction and did not require dose reduction or repetition. She maintained this desensitized state after completion of the initial protocol and completed 5 additional weeks of progesterone therapy without further development of rash, thereby successfully sustaining her pregnancy.

The patient described had no history of cyclic skin eruptions, but rather experienced initial symptoms coincident with the use of exogenous progesterone for IVF, suggesting isolated hypersensitivity to synthetic progesterone. Most patients with APD have prior exposure to exogenous progesterone by way of contraceptives, hormone replacement therapy, or infertility

TABLE I. PIO desensitization protocol

Dose no	Time (h)	Dose (mg)	Dilution	mL
1	0.00	0.001	1:1000	0.02
2	0.25	0.0025	1:1000	0.05
3	0.50	0.005	1:1000	0.1
4	0.75	0.01	1:1000	0.2
5	1.00	0.025	1:1000	0.5
6	1.25	0.05	1:100	0.1
7	1.50	0.1	1:100	0.2
8	1.75	0.2	1:100	0.4
9	2.00	0.5	1:100	1
10	2.25	1	1:1	0.02
11	2.50	2	1:1	0.04
12	2.75	20	1:1	0.4
13	3.00	26.1	1:1	0.52
Total		49.9935		

Full-strength progesterone in oil is 50 mg/mL. Dilutions were made with normal saline. Doses are given every 15 minutes; if any reaction occurs, the dose can be repeated or decreased according to severity.

treatments.[1,3-6] The pathogenesis of ADP is speculative; however, one theory hypothesizes that exogenous progesterone exposure leads to sensitization through generation of progesterone-specific IgE antibodies. Later, cross-reaction of these antibodies with endogenous progesterone occurs through a type I hypersensitivity mechanism as progesterone levels rise in the luteal phase of the menstrual cycle.[1,3-6] The skin has progesterone-specific receptor sites, and antigen may preferentially deposit there, leading to cutaneous symptoms.[4] This immune mechanism is supported by positive skin testing and intramuscular challenges to progesterone.[3,4]

Interestingly, our case is among the few in the literature that describe iatrogenic APD, and she further supports the hypothesis that supratherapeutic doses of exogenous progesterone may induce hypersensitivity. Because progesterone therapy is being administered increasingly for infertility treatment, clinicians should be aware of this rare entity and its iatrogenic causes as well as available treatments. Desensitization provides a therapeutic option for women with APD and is the only treatment for women who desire maintenance of fertility and for women undergoing infertility treatment who must continue progesterone therapy.[1] Desensitization with PIO offers an additional alternative to previously described desensitization with intravaginal or oral progesterone.

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